Less Severe Preoperative Synovitis is Associated with Higher Self-reported Pain Intensity 12 Months After Total Knee Arthroplasty

An Exploratory Prospective Observational Study

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Less severe preoperative synovitis is associated with higher self-reported pain intensity 12 months after total knee arthroplasty – an exploratory prospective observational study

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Abstract

Objectives: Synovitis is one of the possible pain generators in osteoarthritis (OA) and associated with upregulation of pro-inflammatory cytokines, which can lead to worsening of the postoperative pain. This explorative study aimed to investigate the association between perioperative synovitis and self-reported pain 12-months after total knee arthroplasty (TKA) in patients with OA.

Methods: Twenty-six knee OA patients were included in this analysis. Perioperative volume of synovitis in predefined locations was assessed by contrast enhanced magnetic resonance imaging (CE-MRI) and dynamic CE-MRI (DCE-MRI). Perioperative synovitis was assessed histologically from biopsies of the synovium. Highest pain intensity within the last 24-hours (visual analog scale, VAS, 0-100) was assessed before and 12-months after TKA. Patients were divided into a low-pain intensity (VAS≤30) and a high-pain intensity (VAS>30) group based on 12-months postoperative VAS.

Results: The high-pain intensity group had significantly lower perioperative CE-synovitis (P=0.025), DCE-synovitis (P<0.04) and a trend towards lower histologically assessed synovitis (P=0.077) compared to the low-pain intensity group. Perioperative synovitis scores were inversely correlated with pain intensity 12-months after TKA (P<0.05), indicating that more severe perioperative synovitis is associated with less severe pain intensity at 12-months.

Discussion: Higher degrees of perioperative synovitis scores are found to be associated with less postoperative pain 12-months after TKA. Further, correlation analysis revealed that less severe perioperative CE-MRI and DCE-MRI synovitis was associated with higher pain intensity 12-months after TKA, suggesting that CE and DCE-MRI synovitis grades could be used as imaging markers for prediction of chronic postoperative pain after TKA.

The authors declare no conflict of interest.

Introduction

Chronic postoperative pain remains a significant clinical burden[1] and approximately 20% of patients experience chronic postoperative pain after total knee arthroplasty (TKA)[2]. Osteoarthritis (OA) is characterized by inflammation, loss of cartilage, bone remodeling, decreased mobility and pain[3]. Loss of cartilage can be assessed by the Kellgren and Lawrence (KL) score[4] but studies have demonstrated no or low association between KL and self-reported pain[5–9]. Recent studies have found associations between lower KL scores and higher self-reported pain following TKA[10,11], indicating that other factors than the degeneration of cartilage and bone is important for chronic postoperative pain.

Synovitis is present in more than 50% of OA patients[12] and more severe (determined as a thickening of the synovium in predefined locates) synovitis is in most studies to be associated with more severe pain[13]. The direct association between synovitis and pain is unclear but synovitis, assessed from biopsy in patients undergoing TKA, is associated with higher levels of pro-inflammatory cytokines in the synovial fluid [14]. Pro-inflammatory cytokines in the synovial fluid (including interleukin 6 (IL-6)) are known to sensitize the peripheral free nerve-ending leading to peripheral and central sensitization of the nervous system[15] and preoperative measures of central sensitization are associated with chronic postoperative pain following TKA[11,16–18]. Hence, a preoperative measure of synovitis could act as a marker for chronic postoperative pain.

Synovitis can be assessed macroscopically as a thickened hyperemic synovium[19] but histological assessment from synovial biopsies remains the gold standard when assessing synovitis in knee OA[20,21]. However, invasive assessments are not ideal, if synovitis should act as a preoperative marker for postoperative pain. Contrast enhanced magnetic resonance imaging (CE-MRI) following intravenous (i.v.) injection of Gadolinium (Gd) contrast can identify synovitis[22–24] as a thickened contrast-enhanced synovial membrane in predefined locations and separate it from potential joint effusion[23,24] which could act as an preoperative non-invasive marker. In addition to CE-MRI, a dynamic sequence of CE-MRI (DCE-MRI) can be obtain following the i.v injection of Gd contrast[25–27]. As the distribution of Gd depends on the perfusion, DCE-MRI variables can be used as

surrogate markers of perfusion. Thus combining CE-MRI and DCE-MRI provides unique measures to investigate the morphology and perfusion of synovitis in the knee joint[24].

This exploratory study aimed to investigate the association between pre- and perioperative synovitis (CE-MRI, DCE-MRI, and histological) and self-reported pain intensity in patients with knee OA 12 months after TKA.

Materials and Methods

Subjects

In this explorative prospective observational study, patients with severe knee OA with KL scores of 3 and 4 and at least moderate pain measured as maximal knee pain intensity within the last 24 hours above 30 on a visual analog scale (VAS) from 0 mm (no pain) to 100 mm (worst imaginable pain) participated. The maximal pain intensity within the last 24 hours at the 12-month follow-up after surgery was used to define two groups: patients with mild postoperative pain (VAS≤30) were assigned to the low pain group, while patients with moderate-to-severe pain (VAS>30) were assigned to the high pain group, as previously described[17]. All participants were given a verbal explanation of the study, and written informed consent was obtained from each participant before inclusion in the study. The study was approved by the local ethics committee (N-20110031, approved June 27th, 2011, OS was research responsible) and conducted in accordance with the Declaration of Helsinki. Participants were recruited from the Department of Orthopedic Surgery, Aalborg University Hospital, Denmark, upon referral to TKA. Eligibility criteria were as follows: symptomatic, primary knee OA according to the American College of Rheumatology criteria, radiographically confirmed[28]. In case of bilateral KOA, the knee scheduled for TKA was defined as the target knee. Subjects were excluded if any of the following criteria was present: other local (e.g., nerve root entrapment) or generalized pain conditions (e.g., fibromyalgia), any sensory dysfunctions, other significant musculoskeletal disorders (e.g., hip OA), mental impairment or insufficient Danish language skills precluding an informed consent or contraindications for CE-MRI. CE-MRI was not performed if the patient had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. All patients that completed the

pre- and 12 months postoperative evaluations were included in current analysis. The pre-, peri- and postoperative pain management for all the patients included adhere to the Fast-Track Hip and Knee Arthroplasty regime [29].

MRI protocol

MRI of the target knee was performed on a Philips Intera® 1.5 T system. The subjects were scanned in the supine position using a dedicated knee coil. The following MRI-sequences were performed: sagittal T1w turbo spin echo (TSE); sagittal proton density weighted (PDw) TSE; sagittal/axial/coronal PDw SPIR. Just prior to and simultaneously with the i.v injection of 0.1 ml/kg body weight Gd contrast (Gadobutrol) using a power injector (2 ml/s), a sequential sagittal DCE-MRI T1w sequence was performed in 23 slices every 5 s and with 40 repetitions (matrix 352 x 352, field of view (FOV) 180 mm, TE 4.6 ms, TR 8.3 ms, ST 8 mm, flip angle 12º). Following this, the static sagittal T1w TSE sequence was repeated. Total scan time varied between 20 and 30 min. See Riis et al., 2017[30] for more information about the protocol.

Image analysis

A fellow in musculoskeletal radiology (RGCR) performed all MRI assessments, supervised by a senior consultant in musculoskeletal radiology (MB). Both were blinded to the histological and macroscopic data. The DCE-MRIs were analyzed using Dynamika® v.3.2.1 (Image Analysis Group, London, UK) after application of motion correction, regions of interest (ROIs) were drawn manually around the synovium covering the suprapatellar pouch (incl. the biopsy sites) and the medial and lateral recesses on the sagittal DCE-MRI slices. These ROIs were then collapsed into a single volume of interest (VOI) from which the perfusion variables were extracted. The pharmacokinetic variables were calculated using the extended Tofts model[31] and the arterial input function was determined by placing a point-of-interest in the popliteal artery on the DCE-MRI. Heuristic DCE-MRI analysis is based on the signal intensity (SI)-changes over time thus creating time-intensity-curves (TICs). From these TICs various heuristic DCE-MRI parameters can be extracted, such as the initial rate of enhancement (IRE, the upslope on the TIC, i.e. as the relative increase in SI measured in %/s) and the maximum enhancement (ME, dimensionless). Based on the shape of the TIC, Dynamika can automatically assign every voxel to one of four perfusion patterns: no enhancement, persistent (voxels that do not reach a plateau phase), plateau (voxels

that reach a plateau but not a washout phase) and washout (voxels that reach a washout phase). In other words, plateau and washout voxels represent the highest perfused voxels. We converted the number of voxels within the VOI into a volume (ml) of synovitis which was used in the analyses. The volume of voxels with "plateau" or "washout" patterns, the maximum enhancement (ME), i.e., the highest mean signal intensity value relative to the baseline intensity and the initial rate of enhancement (IRE), i.e., the upslope on the TIC measured as the mean relative increase in signal intensity per second (%/s) were extracted. By multiplying Nvoxel (the volume of the highest perfused synovium) with the mean IRE and mean ME (surrogates of the degree of perfusion) respectively, we created two composite variables reflecting both the volume and degree of perfusion (IRE x Nvoxel and ME x Nvoxel, respectively), as described elsewhere[30].

The pharmacokinetic variables were calculated using the extended Tofts model[31] and the arterial input function was determined by placing a point-of-interest in the popliteal artery on the DCE-MRI.

We furthermore used the post-Gd sagittal T1w TSE images to assess synovitis (0-2) according to Guermazi et al., 2011[32] based on the thickness of the synovium in 11 different locations in the knee thereby generating a whole-knee synovitis score (CE-Synovitis), ranging from 0 to 22. The MRI-assessments are described in detail by Riis et al., 2017[30].

Histological assessment of synovitis

Synovial biopsies (1 x 1 cm) were collected intraoperatively by the surgeons in the following locations 1) suprapatellar pouch anteriorly and 2) posteriorly, (3) medial and (4) lateral recesses, (5) most severe synovitis macroscopically and (6) most severe synovitis on CE-MRI. The biopsies were immediately immersed in a formalin solution, numerated and stored until embedment in paraffin. From each biopsy, a representative slice was obtained using a 3 mm microtome and stained with hematoxylin and eosin. A resident in pathology (NMAM) performed all the histological assessments supervised by a senior consultant in pathology (ME). Both were blinded to the imaging and macroscopic data. For each slice, the most severe change was noted (0 - 3) for the following three histopathological qualities according to Krenn et al.[20]: (1) hyperplasia/enlargement of the

synovial lining cell layer, (2) inflammatory infiltration and (3) activation of synovial stroma. For each feature, an average grade from the six biopsies was calculated for each patient. The three averages were then summed, creating a total histology score ranging from 0 - 9 as described by de Lange-Brokaar et al.[33] with higher scores indicating more severe synovitis.

Statistics

The data are presented as means and standard errors (SE) if not otherwise stated. Repeated measures analysis of variance (RM-ANOVA) with a time (preoperative, postoperative) factor and an in-between group (high pain, low pain) factor was used to investigate pre- and 12-months postoperative pain scores between the groups. Post hoc tests were performed in case of significant factors and the Bonferroni correction was added to account for multiple comparisons. Independent sample t-tests were used to compare preoperative data between the two groups. Pearson correlation was used for correlation analysis. All analyses were conducted in SPSS version 25 (IBM corporation©) and $P<0.05$ was considered significant.

Results

Patients were included from November 2011 to June 2012. Preoperatively, 60 persons were included in the study. Unfortunately, the MRI protocol did not include a DCE-MRI sequence in the first 10 persons, who were thus excluded. Due to an eGFR < 60 ml/min/1.73m^2, MRI was not performed in three persons and additionally three persons withdrew their consent. Of the remaining 44 persons, MRI analyses were not feasible in one due to motion artefacts, one person did not undergo TKA and synovial biopsies were not obtained in three. The number of subjects with both preoperative MRI and histological data was therefore 39 and 26 patients returned for follow-up 1-year after TKA.

Demographics

Of the 26 KOA patients, 9 patients (35%) reported 12-month postoperative VAS > 30 (high pain group) and 17 (65%) patients reported postoperative VAS ≤ 30. Patient demographics are listed in table 1. No significant differences were found between the groups regarding preoperative patient demographics.

Pain intensities

Pain intensities pre- and 12-months postoperatively for the low and high pain groups are presented in figure 1. A significant interaction between time and groups (ANOVA: $F(1,24) = 16.539$, $P = 0.001$) found than pain significantly decreased comparing pre- and postoperative pain scores in the low pain group ($P < 0.001$) but not in the high pain group ($P = 0.86$). In addition, no significant differences were found when comparing preoperative pain scores ($P = 0.786$) and the high pain group reported significantly higher pain scores 12 months after surgery compared with the low pain group ($P < 0.001$).

Preoperative synovitis scores

Correlations between preoperative CE-MRI, DCE-MRI and histology scores are displayed in table 2. Significant correlations were found for all four markers.

Preoperative synovitis and chronic postoperative pain

Preoperative findings from histology, CE-synovitis, number of voxels x ME, number of voxels x IRE are displayed in figure 2. Significantly higher preoperative CE-synovitis ($P = 0.025$), number of voxels x ME ($P = 0.037$) and number of voxels x IRE ($P = 0.032$) were found in the low pain group compared with the high pain group. In addition, a trend towards significantly ($P = 0.077$) higher preoperative histology findings were found in the low pain group compared with the high pain group.

Preoperative synovitis correlated to pain at 12-month follow-up

Pooling all data from both patient groups, showed significant Pearson correlations between preoperative CE-synovitis ($R = - 0.455$, $P = 0.022$), number of voxels x ME ($R = -0.528$, $P = 0.007$), number of voxels x IRE ($R = -0.511$, $P = 0.009$) and a trend towards significant between histology findings ($R = -0.384$, $P = 0.053$) and postoperative pain intensity 12 months after TKA. This indicate that more severe preoperative synovitis was associated with less postoperative pain. None of the preoperative synovitis measures were correlated to preoperative pain ($P > 0.13$).

Discussion

This is the first study to use state of the art synovitis assessment with both standard and dynamic contrast enhanced magnetic resonance imaging in combination with histological methods to link synovitis scores with postoperative outcomes in OA patients after TKA.

This exploratory prospective observational study showed that less preoperative synovitis scores are associated with stronger postoperative pain 12 months after TKA, indicating that it could be used as an indicator for pain outcome after knee replacements in patients with osteoarthritis.

Inflammation as a preoperative predictor of chronic postoperative pain

A recent human study found higher synovitis scores and higher levels of synovial fluid IL-6 to be associated with worse pain[14]. In addition, a smaller study found that preoperative upregulation of IL-6 and TNFα in the synovial fluid were associated with poor pain improvement 2-years after TKA[34]. It is noteworthy, that the inflammation might be localized to the knee joint and not necessarily to the blood[35], which might be in contrast to previous animal studies[15]. Animal studies have found that pro-inflammatory cytokines can sensitize the peripheral nerves leading to peripheral and central sensitization[15,36]. Several recent human studies have found associations between preoperative central sensitization and chronic postoperative pain following TKA and total hip arthroplasty[17,18,37]. Together, these studies indicate that measures of upregulated inflammation in the joint could act as a preoperative marker for chronic postoperative pain. Our study adds to this by demonstrating that preoperative synovitis was association low pain at 12 months follow-up after TKA. It is important to note that multiple preoperative factors could influences the risk of chronic postoperative following TKA[38] such as high levels of pain catastrophizing[39], sensitization of the central nervous system[11,17,18,37] or opioid use[40], which have not been controlled for in the current explorative study and could be a limiting factor.

Pain in the knee joint

Knee OA is associated with pain and it is often presumed that higher KL scores is associated with higher clinical pain intensities. This would suggest that the degeneration of cartilage results in pain, but recent studies have found that cartilage is poorly innervated by nociceptors[6] and studies find either low or non-significant

correlations between KL and clinical pain in knee OA[5–8,41]. In fact, patients with low KL scores can display high pain intensities[9] and recent studies have demonstrated that low preoperative KL scores could act as a risk factor for chronic postoperative pain following TKA[10,11], indicating that other factors are contributing to pain. The current study did not find an association between preoperative synovitis scores and preoperative pain but found that lower preoperative synovitis scores were associated with greater chronic postoperative pain. This further indicates that lower radiological assessment of knee pathologies could be associated to chronic postoperative pain following TKA.

In contrast to cartilage, the synovial membrane is densely innervated by nociceptive fibers[6]. Inflammation can sensitize the peripheral nerve-endings, which leads to hyperalgesia[15] and inflammation of the synovial membrane when assessed histologically is associated with pain[14]. Contradicting this, Hill et al., [42] assessed synovitis using CE-MRI and found that synovitis was not associated with pain but progression in synovitis severity was associated with worsening in pain intensity. Petersen et al., [43] assessed synovitis using MRI and found that knee OA patients with no signs of synovitis were more pressure pain sensitive compared to patients with a mild degree of synovitis, which further indicates that pain can be influences by multiple factors other than synovitis. Interestingly, de Lange-Brokaar et al., [44] using CE-MRI to quantify synovitis and found different distribution patterns of synovitis to be associated to different degrees of pain levels and some of these patterns are not associated with pain. In this context, several different scoring systems for synovitis have been developed for OA[32,42,45–48] and previous studies have been utilizing the different scoring systems, which complicates the comparison between studies. The current study, did not investigate synovitis progression or different patterns of synovitis, which may explain the reason for the lack of association between preoperative pain intensities and measures of synovitis. This is the first study to use state of the art synovitis assessment with both CE and DCE-MRI methods showing that lower preoperative synovitis scores are associated with worse chronic postoperative pain levels and this further add to the growing evidence that low levels of preoperative radiological OA pathological measures could act as risk factors for chronic postoperative pain.

Limitations

The current study is limited by the fact that it did not include other relevant measures of inflammatory activity in the knee joint such as cytokine profiling of the synovial fluid. A smaller study[34] found that higher concentrations of IL-6 and TNF-α in the synovial fluid was associated with less pain improvement 2-years following surgery but several larger studies are needed to confirm these findings.

Pain catastrophizing is a major preoperative risk factor for chronic postoperative pain following TKA[38], which was not assessed in the current study and could be an underlying factor, which should be controlled for in future studies.

Postoperative pain is one of the main drives for the development of severe chronic postoperative pain[38,49]. The current study, did not monitor pain in the postoperative phase, which is a limiting factor the interpretation of the results.

The sample size of the current study is low compared to other studies, which aim to investigate preoperative risk factors for the development of chronic postoperative pain. Further, a larger proportion of the patients did not attend the follow-up session, which greatly limits the study. Finally, due to the limited sample size, the statistics in the current study is simplified. Therefore, more studies with robust sample size calculations and predefined statistical analysis plans should be conducted.

Perioperative pain management will affect the risk of chronic postoperative pain[49] and the current study adhered to the guidelines of fast-track surgery for TKA[29]. It is of note that the perioperative pain management will differ according to the patients need, which the explorative current study has not correct for, which limits the interpretation of the results.

Conclusion

The current exploratory prospective observational study of knee osteoarthritis showed that patients with high chronic postoperative pain 12 months after TKA have lower MRI verified synovitis scores and a tendency to

lower histological inflammatory grading in synovial biopsies compared with patients with less severe postoperative pain. Further, analysis revealed that less severe preoperative synovitis was associated with higher postoperative pain intensities 12-months after TKA, indicating that synovitis grade verified with MRI findings may be a candidate for prediction of surgical outcomes after TKA in patients with knee osteoarthritis.

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Figure legends

Figure 1: Pre- and 12-months postoperative pain intensity (VAS points) from 26 knee osteoarthritic patients undergoing total knee arthroplasty divided in to High Pain (VAS > 30) or Low Pain (VAS≤30) at 12-months follow-up. # indicate $P < 0.05$ comparing the groups at 12-months postoperative follow-up. * indicate $P < 0.05$ comparing pre- and postoperative pain scores.

Figure 2: Preoperative findings from histology (A), CE-synovitis (0-22) (B), number of voxels x ME (C) and number of voxels x IRE (D) from 26 knee osteoarthritic patients undergoing total knee arthroplasty divided in to High Pain (VAS > 30) or Low Pain (VAS≤30) at 12-months follow-up. * indicate $P < 0.05$ comparing the high pain group and the low pain group.

	High pain group	Low pain group	P-value
Gender, number (%) female of group	5 (56%)	9 (53%)	P = 0.790
BMI, kg/m^2	29 (2)	30 (1)	P = 0.266
Age, years	64 (4)	70 (2)	P = 0.256
Duration with osteoarthritis, years	11 (3)	18 (4)	P = 0.276
Kellgren & Lawrence, average (range)	3.89 (3-4)	3.94 (3-4)	P = 0.667

Table 1: preoperative gender distribution (percentage), mean (standard error) for body mass index (BMI), age and duration of osteoarthritis and Kellgren & Lawerence scale (radiological measure of osteoarthritis) from the 26 knee osteoarthritis patients included in the study.

	Histology	CE-synovitis	No. voxels x ME	No. voxels x IRE
Histology		R = 0.693 P < 0.001	R = 0.626 P < 0.001	R = 0.512 P = 0.001
CE-synovitis			R = 0.645 P < 0.001	R = 0.612 P < 0.001
N. voxels x ME				R = 0.894 P < 0.001
No. voxels x IRE				

Table 2: Pre- and perioperative pearson correlation matrix analysis of synovitis scores assessed by histology, whole-knee synovitis score based on contrast enhanced magnetic resonance imaging (CE-synovitis) and perfusion of the synovial membrane (Number (No.) of voxels x ME and No. of voxels x IRE).